# RUNX1 prevents oestrogen-mediated AXIN1 suppression and beta-catenin activation in ER-positive breast cancer.

**Journal:** Nat Commun

**Publication Year:** 2016

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**PubMed link:** 26916619

**Funding Grants:** CIRM Stem Cell Biology Training Program

**Public Summary:**
Nearly two-thirds of all breast cancer tumors are estrogen receptor-positive (ER+), yet much remains to be learned about mechanisms underlying disease progression. Three high-throughput sequencing studies of tumor DNA were recently published in the journal Nature (2012), with the hope that they disclose novel targetable disease mechanisms. All three studies reported on recurrent mutations in a gene called RUNX1. However, these studies did not address mechanisms underlying the implied RUNX1-mediated suppression of ER+ breast cancer. By depleting mammary epithelial cells of RUNX1 in cell culture and mouse models, Chimge et al. demonstrate that RUNX1 and estrogens combinatorially regulate the AXIN1 gene, so that AXIN1 protein, a central tumor-suppression hub, goes astray when RUNX1 is lost in breast cancer cells, specifically those with activated ER. Chimge et al. also demonstrate that deregulated AXIN1 in ER+ breast cancer unleashes expression of the oncogenic protein ß-catenin. Further pursuing mechanisms downstream of ß-catenin, Chimge et al. discovered that consequences of ß-catenin deregulation in ER+ breast cancer are completely different from those previously reported in colon and other cancers. Most notably, RUNX1-loss in ER+ breast cancer leads to mitotic deregulation associated with increased ß–catenin levels in the centrosome, an organelle that controls chromosomal segregation during cell division. In summary, recent observations of RUNX1 mutations in tumor biopsies lead Chimge et al. to the discovery that estrogens drive breast cancer by suppressing AXIN1, leading to the unleashing of ß-catenin, which itself deregulates cell cycle control through previously unknown mechanisms. Such estrogen-driven breast carcinogenesis is normally prevented by RUNX1. Upon loss of RUNX1, which occurs according to Chimge et al. in as much as 40% of ER+ breast cancer patients, a carcinogenic mechanism is activated, which can be prevented, at least in part, but targeting AXIN1.

**Scientific Abstract:**
Recent high-throughput studies revealed recurrent RUNX1 mutations in breast cancer, specifically in oestrogen receptor-positive (ER(+)) tumours. However, mechanisms underlying the implied RUNX1-mediated tumour suppression remain elusive. Here, by depleting mammary epithelial cells of RUNX1 in vivo and in vitro, we demonstrate combinatorial regulation of AXIN1 by RUNX1 and oestrogen. RUNX1 and ER occupy adjacent elements in AXIN1's second intron, and RUNX1 antagonizes oestrogen-mediated AXIN1 suppression. Accordingly, RNA-seq and immunohistochemical analyses demonstrate an ER-dependent correlation between RUNX1 and AXIN1 in tumour biopsies. RUNX1 loss in ER(+) mammary epithelial cells increases beta-catenin, deregulates mitosis and stimulates cell proliferation and expression of stem cell markers. However, it does not stimulate LEF/TCF, c-Myc or CCND1, and it does not accelerate G1/S cell cycle phase transition. Finally, RUNX1 loss-mediated deregulation of beta-catenin and mitosis is ameliorated by AXIN1 stabilization in vitro, highlighting AXIN1 as a potential target for the management of ER(+) breast cancer.